Comparative Study Of

BCG Vs BCG + INTERFERON Combination

As Intravesical Therapy in Superficial Bladder Cancer

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Introduction

Superficial bladder cancer constitutes 75-80% of all bladder carcinomas. Various combinations from low stage low grade to high stage and grade tumors occur with widely varying potential to invade and metastasize.

Initial transvesical resection can give us the correct stage and grade based on which further adjuvant therapy is planed. Adjuvant intravesical chemotherapy or immunotherapy has shown significant cancer free survival when compared to TUR alone.

Morales and associates first reported the use of BCG in the treatment of superficial bladder cancer in1976 and since then several papers have reaffirmed the effectiveness of BCG in superficial bladder cancer.

BCG which has proven to be an important agent against Superficial TCC is not with out its own drawbacks. It has wide ranging side effects which limit its use as well as decrease patient compliance. The toxicity is

directly linked to the amount of BCG that is instilled into the bladder. Hence effort has been directed at reducing the toxicity profile of BCG either by reducing the dose of BCG and or by combining BCG with other immunomodulators.

Interferon which is at the forefront of this combination protocol has been found to be relatively effective when used alone or in combination with BCG in vitro and in vivo. But the dosage, the dose of the combination and the treatment schedule has not met with universal consensus. Many combinations from low dose of BCG with high doses of interferon and vice versa have been tried with varying results.

Hence this study has been envisaged with an idea of combining both low dose BCG and low dose interferon and test their efficacy, safety and toxicity profile in the management of superficial bladder cancer.

Aim

The aim of the present work is to do a prospective randomized comparison of 120mgs of BCG against a combination of 60mgs of BCG and 6 million international units of interferon alfa 2b as intravesical therapy in the treatment of superficial bladder cancer.

So the primary end point would be to see whether this combination of low dose interferon and BCG is as efficacious as full dose of BCG.

The secondary endpoints would be to assess the toxicity profile and to see whether this compares favorably with full dose of BCG and to see whether this combination has a synergistic effect, thereby producing any survival benefit or any prevention of progression.

Other parameters like size of the index tumor, multifocality, stage grade, incomplete resection, time to recurrence is also being assessed to see how these parameters impact survival and natural history of the disease

MATERIALS and METHODS

Study design was a prospective randomized trial. 61 patients were totally recruited and randomized into the study over a time frame of 8 months and were subjected to the following regimen. After initial TURBT (May 03 To Dec 03) and stage and grade assessment and a time gap of at least 30 days after TURBT the patients were subjected to intravesical BCG 120mgs (Group A) or BCG 60mg along with 6 million international units of Interferon a2b (Group B) with 60ml of physiological saline and instilled into the bladder.

This treatment was given every week for 6 weeks and every month for 6 months accounting for a total of 12 intravesical instillations and further 3 weekly maintenance dose at the end of 12 months ,18months 24 months 30 months etc.

Each instillation was for a period of two hours in which the patients were advised to lie in prone, supine, left and right lateral positions for half an hour each.

Follow up of the patients included urine cytology for malignant cells, USG abdomen and check cystoscopy every 3months for the first year and every 6 months for the next 2 years and yearly thereafter and upper tract evaluation was done periodically

The strain of BCG that was used was the Danish 1331 strain produced in 40mg vials by the BCG vaccine laboratory, Guindy – Chennai.

Human interferon Alfa 2b, r – DNA (recombinant) was used.

Patient selection

All patients who presented to our unit and were found to have superficial bladder cancer were enrolled into our study. Superficial bladder cancer included CIS, T1, and Ta including all grades (except Ta Grade 1 and 2). All cases excepting CIS were proved by TURBT and for CIS cold cup biopsies were used for histopathology. No additional therapy in the form of resection or fulguration was used for CIS. A thorough history, clinical investigations USG and CT scan with IVP for upper tract evaluation was performed. All cases informed written consent was obtained before commencement of the procedure.

Exclusion criteria

The following exclusion criteria were applied: pregnancy previously diagnosed and treated bladder cancer, recurrent bladder cancers, exposure to previous therapy with interferon in whatever form, previous therapy for pulmonary tuberculosis, muscle invasive bladder cancer and known hypersensitivity to either BCG or interferon. Patients with prostatic urethral involvement were also excluded from the study. Persons with stricture urethra on regular urethral dilatation were also excluded from the study. Multiple superficial TCC with majority of lesions in unresectable areas were also excluded from the study.

Stages Ta with Grade 1 and 2 were also excluded as these tumors are enrolled only in a surveillance protocol in our unit without any further adjuvant therapy.

Response criteria

Response was categorized into complete response, partial response and no response or progression.

Complete response was defined as total resolution of the tumor confirmed with negative biopsy and cytology.

Partial response was defined as same stage and grade recurrence. These cases were usually managed by TUR and then restarting the same treatment schedule.

No response or progression was defined as higher stage and grade recurrence and development of tumor in new areas in the bladder during the treatment schedule. Cases that progressed were taken out of the study and invariably went in for radical cystectomy.

Toxicity evaluation

Toxicity was evaluated by observation by the treating doctors, patient reports and local and systemic reactions. A quantitative bladder symptom questionnaire and a visual analogue scale which was filled in by patients at the time of cystoscopy were used to study the toxicity profile. The severity of the adverse reactions was graded according to a subjective and objective assessment protocol. Discomfort was graded on a visual analogue scale with 1 being least toxic and 5 being the worst. Up to a weeks delay was planned to be allowed for each instillation if the patient was unable to tolerate the drug regimen.

Statistical analysis

Data were entered in excel software and analyzed using SPSS software. To examine the statistical significance difference with categorical variables, the chi-square test was used. Kaplan-Meier survival analysis was done to examine the distribution of times and duration of disease free status after surgery (in months). Censored cases are cases for which the outcome is not known, that are patients are still in follow-up.

Review of literature

Bladder cancer is the second most common urologic malignancy after prostate cancer. On histopathology, 93% of bladder cancers are transitional cell carcinomas, 5% are squamous cell carcinomas, and 2% are adenocarcinomas.

The majority of bladder cancers present as superficial (80%), with only 15% presenting as invasive cancer and 5% as metastatic disease. Superficial bladder cancers are a heterogeneous group of cancers with variable biologic potentials.

Three “sub stages” are defined

Ta — papillary tumor confined to the urothelium),

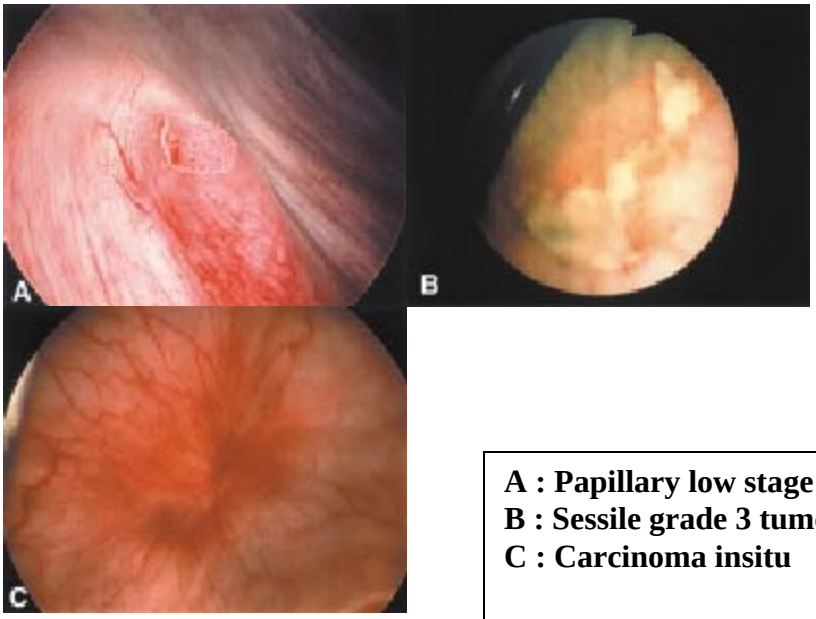
T1 — papillary tumor invading the underlying lamina propria

Tcis (carcinoma in situ) — flat, reddened lesions on cystoscopic appearance with high-grade histologic

Features (i.e., changes throughout the whole thickness of the urothelium, marked loss of polarity, and easily found mitotic figures) but with changes confined to the urothelium

only

Ta	Papillary tumor confined to the urothelium
T1	Papillary tumor invading the underlying lamina propria
Tcis	Flat, reddened lesion on cystoscopic appearance; high-grade histologic features confined to the urothelium



A : Papillary low stage low grade tumor
B : Sessile grade 3 tumor
C : Carcinoma insitu

Diagnosis and Initial Management

The most common clinical presentation is asymptomatic gross or microscopic hematuria. Occasionally, patients present with irritative voiding symptoms:
Dysuria, frequency, and urgency. This symptom complex is highly suggestive of carcinoma in situ. The presence of hematuria is suggestive of cancer in the urinary tract until proven otherwise. Whenever the presence of transitional cell carcinoma is suspected, a full urologic evaluation consisting of cystoscopy, urinary cytology, and intravenous pyelogram is mandatory.

This evaluation allows for assessment of the whole urinary tract since tumor lesions may be located anywhere along the upper urinary tract (calyces, renal pelvis, ureters) or lower urinary tract (bladder and proximal urethra). When a lesion is noted on cystoscopy, the configuration (flat, sessile, or papillary), location (trigone, base, right lateral wall, left lateral wall, dome), size (in centimeters), and number should be noted.

The initial management consists of complete transurethral resection of any visible tumors and selected biopsies of the bladder mucosa including the prostatic urethra. At the time of resection, an examination under anesthesia is performed prior to and following resection. The presence of a palpable mass suggests muscle invasion by tumor.

With cystoscopic and pathologic findings, the clinician can determine if further treatment with intravesical therapy is required. Additional treatment decisions are based on the estimates of risk of recurrence and progression. Patients can be stratified in two groups: low risk and high risk for recurrence and progression

Low-Risk Group

In most cases, patients present either with a bladder tumor for the first time or with a long interval of time without recurrence. On cystoscopy, there may be up to 3 lesions, they could be up to 3 cm in size, and they have a papillary configuration. On histopathology, the lesions do not invade the lamina propria (stage Ta) and are well or moderately differentiated (grade I or II).

High-Risk Group

Patients in this group may present with a bladder tumor for the first time, or they may have had multiple recurrences in a short period of time. On cystoscopy, there may be more than 3 lesions, they may be larger than 3 cm, and they may appear to be less papillary (sessile) in configuration. Unfavorable findings include incomplete resection due to technical problems (such as location of the tumor in an area that is difficult to resect) or diffuse bladder involvement. Pathologically, tumors are high grade and/or invade the lamina propria (T1 lesions). The presence of carcinoma in situ alone or associated with papillary tumors is also an adverse prognostic sign.

Newer molecular markers are being evaluated to more precisely define poor risk. These markers include immunostaining for mutated p53, the presence of aneuploidy, and a high proliferation rate (Ki-67 immunostain-positive tumors).

	Low risk	High risk
Multiple, frequent recurrences	**No**	**Yes**
Appearance	**Papillary, fine stalk**	**Papillary, thick stalk, or sessile**
Size	**3 cm**	**>3 cm**
Number of lesions	**3**	**>3**
Transurethral resection	**Complete**	**Incomplete**
Stage	**Ta**	**T1, Tcis**
Grade	**I-II**	**III**

Approximately 70% to 80% of patients with newly diagnosed bladder cancer will present with superficial bladder tumors (i.e., stage Ta, Tis, or T1). Those who do present with superficial, noninvasive bladder cancer can often be cured, and those with deeply invasive disease can sometimes is

cured by surgery, irradiation, or a combination of modalities that include chemotherapy. Studies have demonstrated that some patients with distant metastases have achieved long-term complete response following treatment with combination chemotherapy regimens.

The major prognostic factors in carcinoma of the bladder are the depth of invasion into the bladder wall and the degree of differentiation of the tumor.

Most superficial tumors are well differentiated. Patients in whom superficial tumors are less differentiated, large, multiple, or associated with carcinoma in situ (Tis) in other areas of the bladder mucosa are at greatest risk for recurrence and the development of invasive cancer. Such patients may be considered to have the entire urothelial surface at risk for the development of cancer. Tis may exist for variable durations. Adverse prognostic features associated with a greater risk of disease progression include the presence of multiple aneuploid cell lines, nuclear p53 over expression, and expression of the Lewis-x blood group antigen.[1-4]

Patients with Tis who have a complete response to bacillus Calmette-Guérin have approximately a 20% risk of disease progression at 5 years; patients with incomplete response have approximately a 95% risk of disease progression.[1]

Several treatment methods (i.e., transurethral surgery, intravesical medications, and cystectomy) have been used in the management of patients with superficial tumors, and each method can be associated with 5-year survival in 55% to 80% of patient's treated.[1, 2, 5]

Invasive tumors that are confined to the bladder muscle on pathologic staging after radical cystectomy are associated with approximately a 75% 5-year progression-free survival rate. Patients with more deeply invasive tumors, which are also usually less well differentiated, experience 5-year survival rates of 20% to 40% following radical cystectomy. When the patient presents with locally extensive tumor that invades pelvic viscera or with metastases to lymph nodes or distant sites, 5-year survival is uncommon, but considerable symptomatic palliation can still be achieved.[6]

Expression of the tumor suppressor gene p53 also has been associated with an adverse prognosis for patients with invasive bladder cancer. A retrospective study of 243 patients treated by radical cystectomy found that the presence of nuclear p53 was an independent predictor for recurrence among patients with stage T1, T2, or T3 tumors.[7] Another retrospective study showed p53 expression to be of prognostic value when considered with stage or labeling index.[8]

Stage I bladder cancer is defined by the following TNM classification:

T1, N0, M0

Patients with stage I bladder tumors can be cured by a variety of treatments, even though the tendency for new tumor formation is high. In a series of patients with Ta or T1 tumors who were followed for a minimum of 20 years or until death, the risk of bladder recurrence following initial resection was 80%.[9] Patients at greatest risk of recurrent disease are those whose tumors are large, poorly differentiated, multiple, or associated with nuclear p53 overexpression[10]. In addition, patients with carcinoma in situ

(Tis) or dysplasia of grossly uninvolved bladder epithelium are at greater risk of recurrence and progression.[9, 11, 12]

Transurethral resection (TUR) and fulguration are the most common and conservative forms of management. Careful surveillance of subsequent bladder tumor progression is important. One retrospective series addressed the value of performing a second TUR within 2 to 6 weeks of the first. [13]

A second TUR performed on 58 patients with T1 disease found that 14 patients (24%) had residual (T1) disease and 16 patients (28%) had muscle invasion (T2). Such information may change the definitive management options in these individuals. Patients who require more aggressive forms of treatment are

those with extensive multifocal recurrent disease and/or other unfavorable prognostic features. Segmental cystectomy is applicable to only a small minority of patients because of the tendency of bladder carcinoma to involve multiple regions of the bladder mucosa and to occur in areas that cannot be segmentally resected.

Intravesical therapy with thiotepa, mitomycin, doxorubicin, or bacillus Calmette Guérin (BCG) is most often used in patients with multiple tumors or recurrent tumors or as a prophylactic measure in high-risk patients after TUR.

Administration of intravesical BCG combined with subcutaneous BCG following TUR was compared with TUR alone in patients with Ta and T1 lesions. Treatment with BCG delayed progression to muscle-invasive and/or metastatic disease, improved bladder preservation, and decreased the risk of death from bladder cancer.[14] Another randomized study in patients with superficial bladder cancer also reports a decrease in tumor recurrence in patients given intravesical and percutaneous BCG compared with controls.[15]

Two nonconsecutive 6-week courses with BCG may be necessary to obtain optimal response.[16] Patients with a T1 tumor at the 3-month evaluation after a 6-week course of BCG and patients with Tis that persists after a second 6-week BCG course have a high likelihood of developing muscle-invasive disease and should be considered for cystectomy.[16 – 18]

A randomized study that compared intravesical and subcutaneous BCG to intravesical doxorubicin showed better response rates and freedom from recurrence with the BCG regimen for recurrent papillary tumors as well as for Tis.[19] Preliminary results of 1 study have shown a possible survival benefit with maintenance BCG after a 6-week induction course.[20]

Another study that compared alternating mitomycin and BCG with BCG alone, both given for 24 months, found that the efficacy was equal, but that the side effects of the combined regimen were slightly less.[21] A similar trial comparing sequential mitomycin and BCG to mitomycin alone also found no major differences in toxic effects or efficacy.[22]

A randomized trial from the Swedish-Norwegian Bladder Cancer Group compared 2 years of intravesical treatment with mitomycin C versus BCG for patients at high risk for recurrence or progression. At 5 years, a significant improvement was noted in disease-free survival with BCG ($P = .04$); however, no difference was observed in tumor progression or overall survival between the 2 arms.[23]

Standard treatment options:

1. TUR with fulguration.[24,25]

2. TUR with fulguration followed by intravesical BCG.[14,15,17,18,21]

3. TUR with fulguration followed by intravesical chemotherapy.[11,21]

4. Segmental cystectomy (rarely indicated).[24]

5. Radical cystectomy in selected patients with extensive or refractory superficial tumor.[26]

6. Interstitial implantation of radioisotopes with or without external-beam irradiation.[27,28]

Treatment options under clinical evaluation:

1. Use of chemoprevention agents after treatment to prevent recurrence.[29]
2. Intravesical therapies.

Background Of BCG Therapy

BCG immunotherapy is currently acknowledged by most urologists to be the best available intravesical treatment available for superficial and in situ transitional cell carcinoma (TCC) of the bladder. With the possible exception of interferon treatment for hairy cell leukemia, which can achieve 90% complete response, BCG treatment appears to be the most effective application of immunotherapy to the treatment of human cancer. With current optimal induction protocols, 82% of patients with carcinoma in situ (CIS) will be expected to have complete response to BCG, and long-term follow-up reveals that 64% of those who respond will remain disease-free for 5 or more years.

The development of BCG immunotherapy in bladder cancer has been the result of both clinical and laboratory research throughout the world.

Background

Holmgren in Sweden was the first to report the use of BCG to treat cancer in humans in 1935 [30]. Some successes occurred in 28 patients, but the report was largely ignored. The profound immunostimulatory effect of BCG, particularly the stimulation of the reticuloendothelial system, led investigators to evaluate the role of BCG in the treatment of tumours in experimental animals in the 1950s. Success in animal trials led to numerous clinical trials, and early reports of these clinical trials were highly encouraging. Unfortunately, subsequent controlled trials in numerous tumour types, many of which were carried out in patients with advanced disease, failed to confirm the benefit of BCG immunotherapy. However, with documented response in patients with melanoma and other cutaneous malignancies, and the obvious analogy to bladder cancer, investigators began laboratory and clinical investigations in the early 1970s.

At the University of California, Los Angeles, the intralesional injection of BCG in a patient with melanoma of the bladder was shown to be feasible [31], and subsequent studies in dogs confirmed that delayed-type hypersensitivity (DTH) responses could be induced with BCG injection in the bladder.[32] At the University of California, San Diego, D Lamm et al

initiated controlled evaluations of BCG immunotherapy in 1973, using a rat bladder tumour model. In this study, repeated BCG treatment significantly reduced tumour growth compared with controls .[33]

Clearly, the most important early contribution to the development of BCG immunotherapy came in 1976, when Morales reported his clinical trial of BCG in 9 patients with recurrent tumours .[34] He observed a 12-fold reduction in the rate of tumour recurrence when patients were used as their own control. The empirically selected treatment protocol, which involved 6 weekly treatments consisting of percutaneous BCG plus an instillation of 120 mg (10^9 colony-forming units [CFU]) BCG diluted in 50 ml physiological saline, retained for 2 hours, was remarkably close to the current optimal treatment regimen. This study was the one on which subsequent controlled trials in the USA were based.

Confirmation of Efficacy in Controlled Trials

Based on Morales' encouraging preliminary data, the US National Cancer Institute funded two prospective randomized trials of BCG versus standard transurethral resection (TUR) alone. D Lamm et al trial was first reported in 1979 [35] and clearly demonstrated that BCG reduced tumour

recurrence in a low-risk population. In a high-risk group in which all patients treated with TUR alone had tumour recurrence by 9 months, Pinsky similarly observed a marked reduction in the rate of tumour recurrence with BCG treatment .[36]

Subsequent follow-up of patients enrolled in these two initial controlled trials have confirmed that the benefit of BCG treatment, unlike that of intravesical chemotherapy, is long term. Protection from tumour recurrence in both studies lasted more than 5 years. The fact that disease progression, as well as recurrence, appeared to be reduced with BCG was impressive, and in 1985,

D Lamm reported a significant reduction in stage progression in patients involved in his initial trial .[37] Herr reported an even more impressive benefit of BCG treatment in 1988. In 86 randomized patients, progression to muscle invasion or metastasis was significantly delayed with BCG treatment ($p<0.02$) and mortality reduced from 32% in controls to 14% with BCG treatment[38] . Subsequent controlled studies by Pagano have confirmed this finding.[39]

Mechanism of Action

BCG is currently the most effective intravesical agent for the treatment and prophylaxis of superficial bladder cancer. BCG is recognized as a nonspecific immune stimulant. Intravesical BCG induces inflammation of the bladder with infiltration of a broad range of cell types. BCG may activate macrophages, T lymphocytes, B lymphocytes, natural killer cells (NK), and killer cells.[40] Intravesical BCG immunotherapy results in cytokine production, including interleukins 1(IL-1), 2(IL-2), and 6(IL-6), interferon gamma, and tumor necrosis factor alpha (TNF-a)[41] which can be measured in the urine for many hours after instillation. McAveray et al.[42] reported that BCG induces a local Type II immunologic response which may be mediated by Interleukin (IL) 4; IL-4, IL-10, the later cytokines may suppress cell-mediated responses. These cytokines also cause a shift to Type I response with the subsequent development of a protective antitumor response.

Ratliff et al.[43] investigated the role of CD_4 and CD_8 lymphokines in the antitumor response of BCG and reported that there is no evidence of induction of protective systemic immunity after BCG. However, they reported a requirement of T-lymphocytes, and CD_4 and CD_8 subsets in BCG-mediated antitumor activity. They concluded that BCG-mediated

antitumor activity is a localized phenomenon. BCG stimulates cytokine production, and this in turn enhances NK cell activity, which increases after BCG immunotherapy.[44,45] Conti et al.[46] reported that immunotherapeutic effects of BCG in bladder cancer patients are related to its capacity to prime macrophages that enhance the release of TNF-a and IL-I alpha, which are involved in tumor killing. BCG produces a T-cell mediated immune response that has been linked to antitumor activity in both humans and mice.[47] The antineoplastic effect of BCG is most likely the result of a combination of enhanced activity of various arms of the immune system.

After intravesical instillation, live mycobacteria attach to the urothelial lining, facilitated by fibronectin, a component of the extracellular matrix.[48] Integrin is required for the direct attachment and internalization of BCG by bladder tumor cells.[48-50] This process leaves bacterial cell surface glycoproteins attached to epithelial cell membranes, and this antigen is thought to mediate the immune response.[51] Tumor cell motility is also thought to be inhibited by BCG through a mechanism involving the BCG-fibronectin-tumor cell interaction.[52] Bladder biopsies following BCG administration show increased expression of human leukocyte antigen (HLA)-Dr antigen on tumor cells and infiltration of tumor and stroma with

lymphocytes, predominantly T helper cells, and macrophages. The helper/suppressor ratio in infiltrating lymphocytes is increased. Changes in peripheral blood are also seen, including heightened immunoproliferative response to BCG antigen and production of specific antibody.[53,54]

Principles of BCG Immunotherapy

To use immunotherapy effectively in the management of bladder cancer or other malignancy, it is important to consider basic principles and understand the differences between immunotherapy and chemotherapy. Currently chemotherapy is limited in specificity, and basically inhibits or destroys rapidly dividing cells. Generally, tumor cell destruction is proportional to drug concentration so treatments are pushed to the limit of tolerance. In contrast, immunotherapy may be either nonspecific or specific. More often than not, optimal responses to immunotherapy are seen at less than the maximum tolerated dose because high doses invoke complex immune regulatory mechanisms. The typical dose response curve with biological response modifiers such as BCG is therefore bell shaped with optimal response occurring at intermediate doses. [55]

The optimal dose of BCG remains to be defined, and may, like the optimal treatment schedule, vary from patient to patient. Current data suggest that intravesical doses between one hundred million (1 x 108) and one billion (1 x 1010) colony-forming units (CFU) are effective, but responses have been reported with doses as low as 10 million CFU or 1 mg BCG.[56] The wide variation in effective clinical doses probably relates to the mode of administration. In intravesical instillation, only those organisms that attach to the bladder wall stimulate an immune response. Therefore, consideration must also be given to avoid administration of medications that can limit the effectiveness of the dose given. Agents that inhibit clot formation reduce fibronectin expression, which may reduce BCG attachment, immune stimulation, and antitumor activity.[57 - 59] Similarly, concern has been raised that administration of antitubercular antibiotics such as isoniazid (INH), which inhibit intravesical BCG attachment and immune stimulation in the guinea pig model[60], may also reduce the efficacy of BCG therapy. However, Stassar et al.[61] reported that INH does not impair the local immunological stimulation after intravesical BCG. Until additional data becomes available, INH, trimethoprim/sulfamethoxazole, and quinolones should be used with caution in patients receiving BCG. However, these

antibiotics should be used without hesitation to treat the side effects of BCG or intercurrent infection.

Efficacy of BCG Immunotherapy

Long-term follow-up studies have consistently demonstrated prolonged protection from tumor recurrence by BCG[62-64] as well as increasing evidence to suggest that optimal BCG intravesical immunotherapy also reduces tumor progression and mortality.[62-65] All six clinical studies comparing surgery alone with intravesical BCG immunotherapy demonstrated a highly significant advantage of BCG treatment [65-70]. Direct randomized comparisons of BCG immunotherapy with intravesical chemotherapy have also demonstrated a statistically significant decrease in tumor recurrence rate with BCG compared with thiotepa, doxorubicin, and mitomycin C (MMC)[71-78].

The Southwest Oncology Group recently compared TICE BCG (50mg) and MMC (20mg) in 469 randomized high-risk patients with stage Ta or T1 disease.[77] Both treatments were given weekly for six weeks then monthly for one year. A 20mg dose of MMC was previously reported to be the optimum dose [78]. In the MMC arm, tumor reoccurred in 33% of patients

with a median time to recurrence of 18.4 months. With a median follow-up of 30 months, 60% of patients in the BCG arm were without tumor recurrence as opposed to 46% of patients in the MMC arm (p=0.017). No toxicity was seen in 18% of the BCG arm or in 30% of the MMC group p<0.003). Melekos et al.[79] reported a recent series of 161 patients enrolled in a three-arm study of intravesical prophylaxis with epirubicin versus BCG versus transurethral resection (TUR) alone. Lamm et al reported that 60% of epirubicin-treated patients, 68% of BCG-treated patients, and 41% of control subjects remained free from recurrences at a median follow-up of 33 months. Epirubicin and BCG were both superior to TUR alone; however, BCG was significantly better than epirubicin in preventing recurrence of stage T1 and high-grade tumors. Cookson and Sarosdy[80] also demonstrated the effectiveness of BCG in high-risk stage T1 patients in their trial; 91% of those treated with intravesical BCG immunotherapy were free of disease at a meanfollow-up of 59 months.

The effect of BCG on tumor progression has been investigated in three randomized studies, each of which found a statistically significant reduction in progression to muscle invasion or metastasis. Lamm demonstrated a reduction in progression to muscle invasive disease in 8% of controls

compared to 3% in the BCG group.[65] This positive impact on progression has resulted in improved survival. A controlled trial from Memorial Sloan-Kettering showed persistent reduction in both tumor recurrence and progression after ten years follow-up. However, the reduction in tumor progression did not extend to fifteen years. Overall, 53% of high-risk patients had progression with a disease-specific survival of 63%. Thus, even after apparent successful treatment with BCG, patients remain at risk for progression, recurrence, and mortality and require vigilant long-term surveillance. In another report, Herr et al.[81] reported that within a median follow-up of eight months, mortality rate was reduced from 32% in TUR alone patients to 14% in BCG-treated patients ($p<0.032$). Herr and associates reported that BCG improved a five-year survival to 87% versus 63% for TUR ($p=0.016$).[64] This author has also reported that cancer deaths were reduced from 37% to 12% ($p<0.01$) and that the cystectomy rate was reduced from 42% to 26% ($p<0.0001$) in patients with BCG.[81] Nadler et al.[63] demonstrated the durability of a single course of BCG which kept 28% (29/104) of the patients tumor-free at 11 years. However, of the 66 patients who received a second six-week course of BCG for recurrent tumors after failing the intravesical six-week course, 27(41%) remained tumor-free at 11 years. Witjes et al.[82] confirmed that effectiveness of BCG in reducing tumor

progression in high-risk patients who had failed prior intravesical chemotherapy for recurrent superficial TCC.

BCG is also effective in the intravesical treatment of CIS. With over 1,000 patients from several series, the average complete response rate of CIS to BCG is in excess of 70%.[83] By comparison, complete response rates for chemotherapy average less than 50%, and in general, fewer than 20% of patients treated with chemotherapy remain disease-free long-term.[62]

In contrast to intravesical chemotherapy, data suggest that maintenance therapy with BCG improves long-term results. In a recent report by the Southwest Oncology Group[77] with optimal BCG immunotherapy for recurrent superficial transitional cell carcinoma (CIS, Ta, T1), the complete response (CR) rate was 87% and long-term disease-free status was maintained in 83% of patients. In CIS patients treated with BCG, the complete response at six months post-therapy is increased from 73% to 87% ($p<.04$) with three additional instillations given at six monthly intervals for maintenance.[62] Maintenance BCG using three weekly instillations increased long-term disease-free status from the expected 65% to 83%. In patients with papillary TCC, maintenance BCG given in a series

of three weekly treatments at three months, six months, and every six months for three years, dramatically reduced tumor recurrence ($p<.0001$) when compared with a single six-week course .[85] Long-term disease-free status was increased from 50% in the induction-only group to 83% in the maintenance therapy group ($p<0.000001$). More importantly, this maintenance therapy has resulted in statistically significant improvement of patient survival as compared to induction-only.

In 391 randomized patients, the excellent 86% survival at four years observed with induction therapy was improved to 92% in patients receiving maintenance BCG ($p<0.04$)[85]. The current recommended maintenance BCG regimen ñ and the only regimen found to be superior to a single, six-week induction ñ employs three weekly instillations of 105 to 108 CFU of Connaught BCG, three months after initiation of treatment.[85] Three weekly instillations are repeated at six monthly intervals for three years. The second or third weekly maintenance treatment is given only if the preceding instillation was without increased side effects. Investigators have reported that in low-dose BCG, 27mg/3x108 CFUs were efficacious, yielding a CR of 84%,[68] and some have seen a reduction in toxicity.

It has been suggested that the efficacy of BCG can be improved further by high-dose vitamins[89]. Lamm et al.[86] reported that daily high-dose vitamins A, B6, C, and E versus recommended daily allowances (RDA) produced further protection from recurrence in patients treated with BCG. The five-year estimates of tumor recurrence were 91% in the RDA group and 41% in the mega dose vitamin group. Overall recurrence was 24 of 30 (80%) patients in the RDA group, and 14 of 35 (40%) in the high-dose arm[86]. Further research is needed to confirm this study and identify which specific vitamins offer the protection from tumor recurrence. Other attempts to improve BCG immunotherapy, such as the addition of intradermal BCG inoculation, have not yet been successful.[86]

Complications of BCG Intravesical Therapy

Intravesical BCG presumably stimulates an immune response to the tumor and thus is associated with unique side effects. Dysuria and urinary frequency are expected as a consequence of the inflammatory response, and cystitis is the most frequent adverse reaction-occurring in up to 90% of cases.[87,88] Hematuria may occur with cystitis and is seen in one-third of patients.[88] Irritative bladder symptoms are unlikely in the week after the first intravesical BCG.[88] Side effects of BCG generally increase with successive

treatments, unless the dose of antibiotics is reduced or prophylactic antibiotics are given. Patients with symptoms lasting more than 48 hours can be treated with 300mg INH daily.[91] This treatment is continued only while the symptoms of hematuria and cystitis persist and is reinstituted one day before subsequent BCG instillation and continued for three days. According to Stassar and associates[61], INH does not impair the local immunological stimulation after intravesical BCG or the efficacy of BCG. BCG treatments are postponed until all side effects from previous instillations have resolved. BCG is a live organism, and even though virulence has been dramatically attenuated, regional or systemic infection may occur.

BCG organisms usually are gone within a few days of instillation but have been reported to persist in the urinary tract for at least 16.5 months after intravesical BCG.[90] Initial estimates of the incidence of BCG sepsis were in the range of 0.04% and 10 patients died following intravesical BCG.[87] The incidence of sepsis has dropped dramatically after the precaution of not administering BCG after traumatic catheterization or in the presence of continued symptoms of BCG infection. When BCG sepsis does occur, we now recommend INH 300mg, rifampin 600mg, and prednisone 40mg daily. Prednisone is continued until sepsis abates and is then tapered gradually over the next two to four weeks. Rifampin and INH are continued

for three to six months, depending on the severity and duration of the reaction. Animal studies have confirmed that this regimen significantly improves survival[89] and no patient receiving this regimen has died of BCG sepsis. The diagnosis of BCG sepsis is made by clinical presentation with high fever, shaking chills, and then hypotension. It is important to proceed with antibiotic treatment without waiting for culture results when systemic BCG infection is suspected. Typically, cultures are negative, even in the face of clinical sepsis. Molecular techniques to identify BCG DNA may prove useful in the future.[91]

BCG versus Intravesical Chemotherapy

In a randomized prospective comparison, Brosman was the first to demonstrate that BCG treatment was superior to intravesical chemotherapy with thiotepa [92]. In his study, a 6-week course of weekly instillations followed by monthly BCG treatment resulted in a remarkable 0% recurrence with BCG treatment compared with 47% recurrence with thiotepa.

In a Brazilian study comparing high doses of oral BCG (Moreau RI) with thiotepa, Netto and Lemos also found high-dose oral BCG to be superior to thiotepa chemotherapy [93].

BCG has similarly been compared with intravesical doxorubicin in a Southwest Oncology Group (SWOG) study. In the first report of this study, BCG was found to be superior to doxorubicin in both the treatment of CIS and the prophylaxis of recurrent TCC [94]. In CIS, complete response was initially seen in 47% of 57 doxorubicin-treated patients and 71% of 52 BCG treated patients. In papillary TCC, tumour recurrence was reduced from 79% in 67 doxorubicin-treated patients to 57% in 60 BCG treated patients. Subsequent long-term follow-up of these patients has provided further evidence of the long-term benefit of BCG treatment [95].

With an average follow-up of 65 months, it is now estimated that only 18% of patients with CIS treated with doxorubicin will be disease-free for 5 years, compared with 45% of those treated with BCG. Of patients with CIS who had complete response to BCG, 64% remained disease-free for 5 or more years. In patients with TA or T1 tumours, 17 and 37%, respectively, are estimated to remain disease-free for 5 years.

Maintenance BCG

As previously stated, the 6-week treatment schedule originally conceived by Morales is remarkably close to the optimal schedule. In uncontrolled trials, however, Kavoussi and associates reported evidence that a single 6- week course of intravesical BCG was suboptimal[96] .

'Response', which included eradication of CIS or residual papillary tumour as well as prevention of tumour recurrence, was seen in 38% of patients treated with a single 6- week course and 60% of patients treated with a second 6- week course. The obvious assumption that a continuous 12-week course (as described by Brosman) is superior to 6 treatments, surprisingly, proved to be incorrect. The dose-response curve of BCG, like that of many biological response modifiers, is bell shaped [97]. Excess BCG can, infact, reduce the antitumour response. In subsequent studies, the recurrence rate with a continuous 12-week course of BCG was high, and evaluation of the immune response by in vitro immunoproliferative assays demonstrated an actual reduction in immune stimulation in these patients .

Three studies have reported comparisons of maintenance and nonmaintenance therapy. In D Lamm's initial report, patients who were originally randomized to no treatment were offered maintenance BCG [98]. A 4-fold reduction was observed in the rate of tumour recurrence, but not incidence, in the maintenance group. In a properly randomized high-risk population of 93 patients, Badalament gave 6-week treatments with or without monthly maintenance instillations [99]. In that study, there was no reduction in the incidence or time to onset of tumour recurrence. The rate of tumour recurrence did appear to be reduced with maintenance, from 0.148 tumours/month in the nonmaintenance group to 0.071 tumours/month with maintenance BCG, but this difference was not statistically significant.

In a similar smaller study, Hudson evaluated instillations every 3 months as a maintenance schedule and again saw no significant reduction in the incidence of tumour recurrence [100]. Animal studies have confirmed that retreatment, as expected, improves the antitumour response when given at a time when the initial immune stimulation has waned .[101]

The controversy should soon be answered, as 550 patients enrolled since 1985 have entered a SWOG comparison of maintenance and non-maintenance BCG therapy.

Carcinoma in situ

Multiple trials have demonstrated the efficacy of BCG in the treatment of CIS. Complete response rates average over 70%, and the duration of response in most studies has been excellent. With an average response rate of 70% or more, it is difficult to demonstrate statistically significant improvement. Surprisingly, the SWOG study comparing maintenance and nonmaintenance BCG, with only 150 randomized CIS patients, was able to demonstrate significant improvement in complete response [102]. In patients given 6 weekly intravesical plus percutaneous Connaught BCG treatments, complete response at 3 months was 61% in the nonmaintenance group and 56% in the maintenance group (not significantly different). With no additional BCG in the nonmaintenance group an additional 9% of patients went on to achieve a complete response by 6 months after initiation of treatment, yielding the expected 70% complete

response rate. With just 3 additional weekly BCG treatments at 3 months, complete response increased by 26% by 6 months ($p<0.02$), yielding an overall complete response rate of 82% ($p<0.04$), This ‘6 plus 3’ regimen (i.e. a normal 6-week induction schedule followed by a 6-week rest, then a further 3 weekly treatments) must, now be considered the optimal induction schedule for patients undergoing BCG treatment for carcinoma of the bladder.

Extensive evaluations of BCG immunotherapy confirm that BCG is the treatment of choice at this time for patients with CIS and potentially aggressive stage TA and T1 TCC of the bladder. Long-term randomized controlled trials confirm that, unlike chemotherapy, the benefits of BCG treatment are long term, and can be translated into a pro-longed decrease in the incidence and rate of tumour recurrence, tumour progression, need for cystectomy, and mortality from bladder cancer. Controlled comparisons with intravesical chemotherapy confirm the superiority of BCG over thiotepa and doxorubicin. While the optimal treatment schedule is still under investigation, a statistically significant increase in complete. response is demonstrated when an additional 3 weekly treatments are given at 3 months after initiation of the standard 6 weekly treatments.

Maintenance BCG will not be needed until the beneficial immune response from induction has waned. The value of maintenance BCG treatments at 6-month intervals is under investigation. In experienced hands, BCG immunotherapy is very safe and highly beneficial to patients who are at risk of multiple recurrences or progression of bladder cancer.

Interferon Alfa in The Treatment Of Superficial Bladder Cancer

Interferon-Alfa (IFN-a) is a biological response modifier that has both direct and indirect action against transitional cell carcinoma (TCC), the most common type of bladder cancer. While intravesical IFN-a monotherapy for superficial bladder cancer has limited total effectiveness vis-a-vis chemotherapy or BCG, it can induce long term remissions even in patients that have failed other forms of therapy and does so with a very favorable toxicity profile causing little to no cystitis.

Recently, combining intravesical IFN-a with chemotherapy or BCG is emerging as a new treatment strategy. Preliminary studies of IFN -a plus Mitomycin suggest additive efficacy.

Combination therapy of IFN-a with BCG appears especially promising. As a mixed intravesical preparation, these two agents are completely biocompatible.

Experimental testing of BCG/IFN-a combination therapy demonstrates a favorable profile on all aspects of the BCG/tumor/immune system interaction. Direct toxic effects of BCG on human bladder cancer lines is enhanced by the addition of IFN-a. The combination also synergistically enhances direct cytokine production by tumor cells, reduces proliferation and upregulates tumor surface markers including histocompatibility antigens and the apoptotic orchestrator Fas. This makes the tumor a better target for immune cell recognition and destruction. Furthermore, IFN-a strongly polarizes the human cellular immune response to BCG in the direction of the favorable T-helper type one (TH1) pathway by down-regulating the antagonistic cytokine IL-10 while upregulating the expression of TNF-a, IL-12, and IFN-gamma. Substantial amplifications in IFN- production are achieved against human lymphocytes during in vitro testing, averaging approximately 40-fold while allowing up to a 100-fold reduction in BCG dose. This feature of IFN-a essentially enhances the body's natural immune response to BCG.

Safety and efficacy studies of combination BCG plus IFN therapy in animal models are similarly encouraging. IFN-ß, closely related to IFN-a, protects against infection by a related mycobacterial pathogen MAI. BCG plus IFN-a or BCG plus the interferon inducer bropiramine are more effective than either agent alone in the murine MBT-2 and MB-49 bladder cancer models.

Sever et al pilot clinical studies using combination intravesical immunotherapy against superficial bladder cancer have shown promising results. Bercovich (1995) found half dose BCG plus low-dose (10 MU) IFN-a-2B to provide equivalent tumor prophylaxis to full dose BCG but with reduced toxicity. Stricker (1996) reported complete and partial response rates at 12 months for 9/12 and 2/12 patients, respectively, all with aggressive histology. Half dose BCG was given together with IFN- a-2B titrated from 10-100 MU with no serious adverse events. Esuvaranathan (2000) has reported a reduction of recurrence rate from 50% to 30% to 10% at 19 months in a randomized study of 8 0 patients treated with full-dose BCG vs. 1/3 dose BCG vs. 1/3 dose BCG plus 10 MU IFN -a, respectively. Patient tolerance was also improved in the combination arm.

The early results of an open-label combination study by O'Donnell (2000) in 38 high risk patients with superficial TCC that had all previous failed BCG is similarly encouraging. Using 50-100 MU of IFN-a-2B plus BCG in doses ranging from full to 1/100th standard dose, titrated down by prior exposure and tolerance especially during the maintenance phase, complete response rates at 26 months median follow-up is 56% even for patients that have failed BCG monotherapy two or more times before. Toxicity has been no different than with BCG alone. Urinary IFN- levels are enhanced or maintained at high levels during therapy.

The use of IFN -a as part of a multidrug cytotoxic chemotherapeutic regimen for advanced urothelial cancers remains provocative. The initial reports of Logothetis et al. showing 30% and 60% PR with IFN-a combined with 5-FU or 5-FU plus platinum, respectively, have not yet been repeated. Parnis (1997) found IFN -a plus cisplatinum to be historically equivalent to cisplatinum alone (35% PR) in a phase II trial involving 22 patients.

RESULTS AND DISSCUSSION

Patient demographics

The results and analysis of the data on 31 patients who underwent intravesical therapy with only 120 mgs of BCG (GROUP A) and 30 patients who underwent intravesical therapy with 60mgs of BCG and 6 MIU of Interferon alfa 2b (GROUP B) are described in this section.

An over view of the demographics of the study population is shown first followed by the results of the study.

Sex distribution

Table 1: Sex distribution

SEX	GROUP				Total	
	A		B			
	Count	%	Count	%	Count	%
Female	15	48.39	8	26.67	23	37.70
Male	16	51.61	22	73.33	38	62.30
Total	31	100.00	30	100.00	61	100.00

Age distribution

Table 2: Age Distribution

Age	GROUP				Total	
	A		B			
	Count	%	Count	%	Count	%
35 - 45	3	9.68	3	10.00	6	9.84
45 - 55	6	19.35	7	23.33	13	21.31
55 - 65	9	29.03	10	33.33	19	31.15
65 - 75	9	29.03	4	13.33	13	21.31
75 - 85	4	12.90	6	20.00	10	16.39
Total	31	100.00	30	100.00	61	100.00

Study population was a total of 61 patients out of which 38 males and 23 females were present. Group A had equal male and female distribution while group B had a skew towards males with 73 males and 27 females.

The mean age group was 62 years and majority of the patients in both groups (A and B) were in the 55 – 65 yrs of age. The next major group was 65 to 75 yrs with 13 patients.

Tumor stage distribution

Table 3: Tumor stage distribution

STAGE	GROUP				Total	
	A		B			
	Count	%	Count	%	Count	%
CIS	8	25.81	8	26.67	16	26.23
T1	19	61.29	19	63.33	38	62.30
TA	4	12.90	3	10.00	7	11.48
Total	31	100.00	30	100.00	61	100.00

62% of the patients were in T1 while 26% were in CIS and the rest were in the Ta group.

All patients who had Ta with grades 1 and 2 were excluded from the study.

Grade distribution

Table 4: Grade Distribution

GRADE	GROUP				Total	
	A		B			
	Count	%	Count	%	Count	%
CIS	8	25.81	8	26.67	16	26.23
G1	4	12.90	4	13.33	8	13.11
G2	13	41.94	11	36.67	24	39.34
G3	6	19.35	7	23.33	13	21.31
Total	31	100.00	30	100.00	61	100.00

As can be seen from this table the study population had a healthy mix of all grades with 39% grade 2 tumors and 21% being grade 3 and 13 % was grade 1. The remaining 26 % was CIS tumors. So this table shows that there was no particular grade that was able to skew results and the maximum was CIS and Grade 3 tumors combined.

Adverse factors

Size more than 3 cms

Table 5: Size

SIZE	GROUP				Total	
	A		B			
	Count	%	Count	%	Count	%
< 3 cms	15	48.39	10	33.33	25	40.98
> 3 cms	16	51.61	20	66.67	36	59.02
Total	31	100.00	30	100.00	61	100.00

Excluding CIS patients all other patients with Ta and Ti group were taken up for this evaluation and out of these tumors nearly 60 % were more than 3 cms in size at the time of resection.

67 % of group B had size more than 3 cms compared to only 51% of Group A.

Hence more number of patients in BCG + IFN group had this adverse prognostic factor.

Multifocality

Table 6: Multifocality

MULTIFOCALITY	GROUP				Total	
	A		B			
	Count	%	Count	%	Count	%
< 3 area	24	77.42	20	66.67	44	72.13
> 3 area	7	22.58	10	33.33	17	27.87
Total	31	100.00	30	100.00	61	100.00

72 % of the patients had lesions than were not multifocal and only 27 % had multifocality.

But out of this, group B had 33% of its total with multifocality while group A had only 22%.

Hence more number of patients in BCG + IFN group had this adverse prognostic factor.

Incomplete resection

Table 7: Completeness of resection

RESECTION	GROUP				Total	
	A		B			
	Count	%	Count	%	Count	%
Complete	31	100	28	93.33	59	96.72
Incomplete			2	6.67	2	3.28
Total	31	100	30	100.00	61	100.00

Only 2 patients had incomplete resection with a small portion being left behind in than anterior wall close to the bladder neck. Both these patients belonged to the BCG + IFN group. One of the exclusion criteria was to exclude extensive superficial tumors that precluded complete resection. But these two patients more than 90% of the growth were resected and hence were considered candidates for the study.

Appearance

Table 8: Appearance

APPEARENCE	GROUP				Total	
	A		B			
	Count	%	Count	%	Count	%
CIS	8	25.81	8	26.67	16	26.23
PAPILLARY	21	67.74	19	63.33	40	65.57
SESSILE	2	6.45	3	10.00	5	8.20
Total	31	100.00	30	100.00	61	100.00

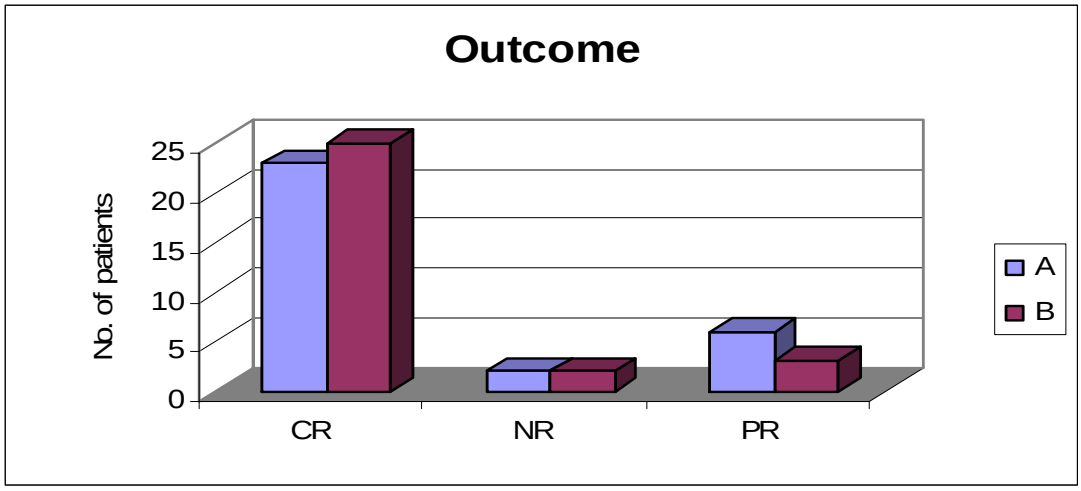
Majority of the patients had papillary growth – 65% while the next major group was CIS

With about 26% and about 8% had sessile growths. None of our patients had both a combination of CIS and papillary growths.

Response to treatment

Table 9: Response

RESPONSE	GROUP				Total	
	A		B			
	Count	%	Count	%	Count	%
CR	23	74.19	25	83.33	48	78.69
NR	2	6.45	2	6.67	4	6.56
PR	6	19.35	3	10.00	9	14.75
Total	31	100.00	30	100.00	61	100.00



Complete response for both the groups combined with a minimum follow up of 21months and a maximum follow up of 28months with a combined total combined follow up of up to 1431 months. The complete response was 78 % with partial response about 14 % and no response about 6% at the end of the study period.

Most of the recurrences were within 6 months of the first instillation. No response patients were diverted to radical cystectomy.

Partial response patients underwent second TURBT and were put on the same protocol of intravesical chemotherapy.

When group A (BCG) is taken, complete response is about 74% and partial response is 19%.

Group B (BCG + IFN) complete response is 83% and partial response of 10%.Both groups had a failure rate of 10 %(no response – cystectomy)

This important table shows us that group B had a higher complete response rate when compared to the group A. This difference assumes significance when we consider that group B had more adverse factors as shown in the previous pages.

Recurrence

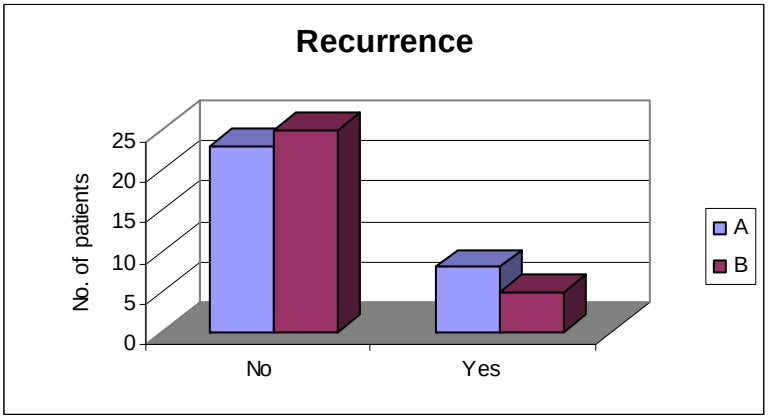


Table 10: Recurrence

RECURRENCE	GROUP				Total	
	A		B			
	Count	%	Count	%	Count	%
No	23	74.19	25	83.33	48	78.69
Yes	8	25.81	5	16.67	13	21.31
Total	31	100.00	30	100.00	61	100.00

Here we see that 26 % of BCG group had recurrences while only 16% of BCG + IFN had recurrences.

Stage and grade wise response

Table 11: Stage and response

RESPONSE	STAGE						Total	
	CIS		T1		TA			
	Count	%	Count	%	Count	%	Count	%
CR	13	81.25	31	81.58	4	57.14	48	78.69
NR	2	12.50	2	5.26			4	6.56
PR	1	6.25	5	13.16	3	42.86	9	14.75
Total	16	100.00	38	100.00	7	100.00	61	100.00

Grade 3 tumors have fared badly in both the groups. But we also see that stage wise Ta tumors have not fared well even though they are only Ta when compared to T1. This can be explained by the fact that only TaG3 tumors are included in the study while T1G1 and G2 tumors can skew the results in favor of T1.

Table 12: Grade and response

RESPONSE	GRADE								Total	
			G1		G2		G3			
	Count	%	Count	%	Count	%	Count	%	Count	%
CR	13	81.25	7	87.50	22	91.67	6	46.15	48	78.69
NR	2	12.50					2	15.38	4	6.56
PR	1	6.25	1	12.50	2	8.33	5	38.46	9	14.75
Total	16	100.00	8	100.00	24	100.00	13	100.00	61	100.00

$P < 0.05$

Stage for stage Grade is more important and grade for grade stage is most important. The order of priority should be stage and then grade of tumors.

Size and response:

Table 13: Size and response

RESPONSE	SIZE				Total	
	< 3 cms		> 3 cms			
	Count	%	Count	%	Count	%
CR	23	92	25	69.44	48	78.69
NR	1	4	3	8.33	4	6.56
PR	1	4	8	22.22	9	14.75
Total	25	100	36	100.00	61	100.00

Table 14: Multifocality and response

RESPONSE	MULTIFOCALITY				Total	
	< 3 area		> 3 area			
	Count	%	Count	%	Count	%
CR	34	77.27	14	82.35	48	78.69
NR	3	6.82	1	5.88	4	6.56
PR	7	15.91	2	11.76	9	14.75
Total	44	100.00	17	100.00	61	100.00

Tumors more than 3 cms in size have fared badly with only 70 % complete response and tumors with less than 3 cms have had 90% complete response.

Incomplete resection and response

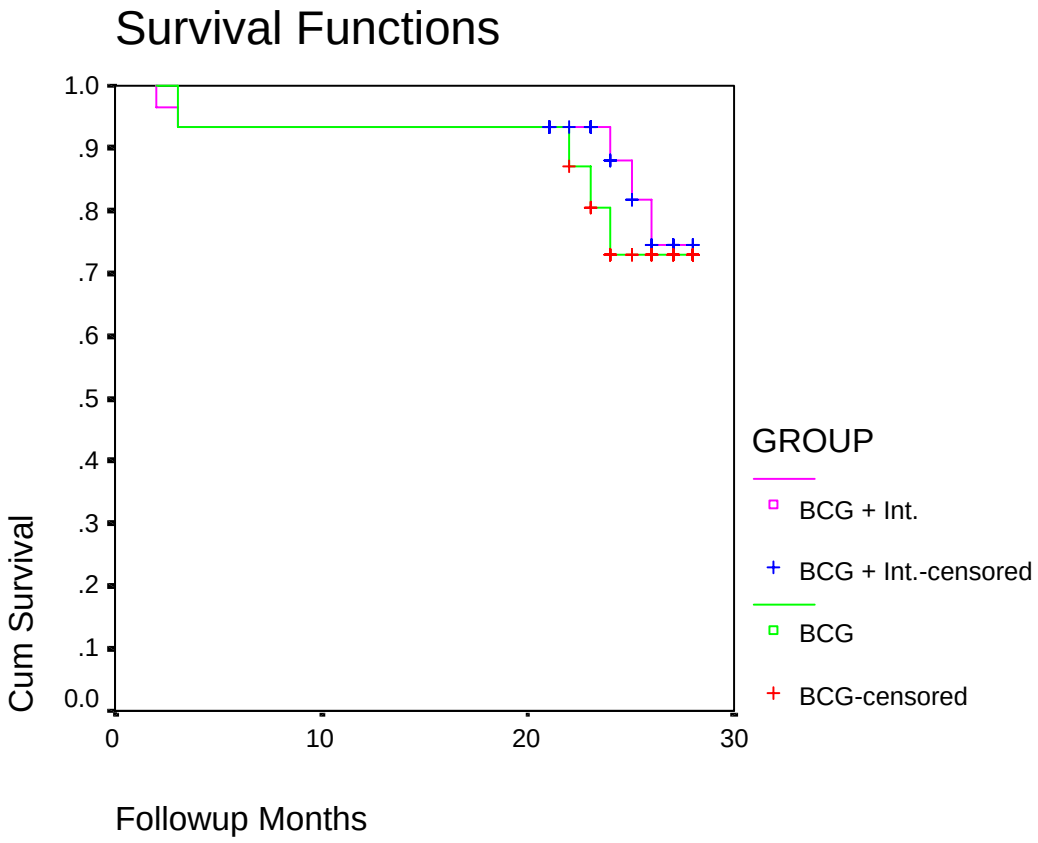
Table 15: Incomplete resection and response

RESPONSE	RESECTION				Total	
	Complete		Incomplete			
	Count	%	Count	%	Count	%
CR	48	81.36			48	78.69
NR	4	6.78			4	6.56
PR	7	11.86	2	100	9	14.75
Total	59	100.00	2	100	61	100.00

$P < 0.05$

Incompletely resected tumors fared badly. Only 2 patients had incomplete resection and both the patients had a recurrence.

Survival function



Kaplan – Meier curve for the above 2 groups show a slightly better result for BCG + IFN vs. BCG alone group. Though this may not be statistically significant a longer follow up may yield better results. Even so the primary hypothesis that half dose BCG + IFN combination is equally if not better effective than BCG alone.

Toxicity profile

Table 16: Hematuria

HEMATURIA	GROUP				Total	
	A		B			
	Count	%	Count	%	Count	%
No	22	70.97	28	93.33	50	81.97
Yes	9	29.03	2	6.67	11	18.03
Total	31	100.00	30	100.00	61	100.00

P < 0.05

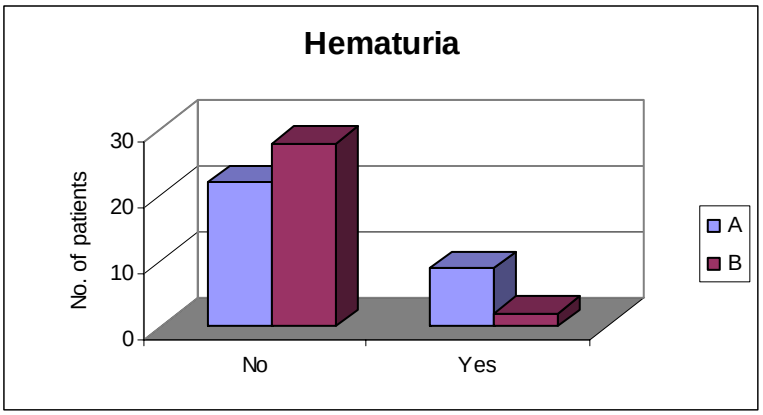


Table 17: Fever and chills

FEVER AND CHILLS	GROUP				Total	
	A		B			
	Count	%	Count	%	Count	%
No	21	67.74	24	80.00	45	73.77
Yes	10	32.26	6	20.00	16	26.23
Total	31	100.00	30	100.00	61	100.00

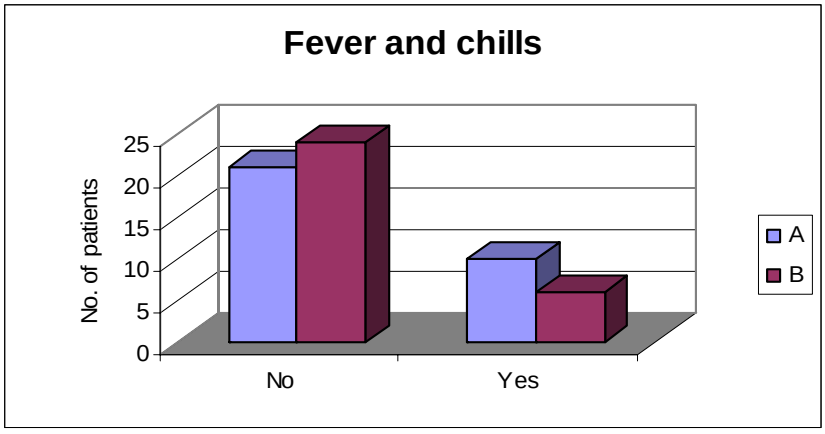


Table 18: Myalgia etc

MYALGIA, MALAISE, ARTHRALGIA,	GROUP				Total	
	A		B			
	Count	%	Count	%	Count	%
No	23	74.19	29	96.67	52	85.25
Yes	8	25.81	1	3.33	9	14.75
Total	31	100.00	30	100.00	61	100.00

$P < 0.05$

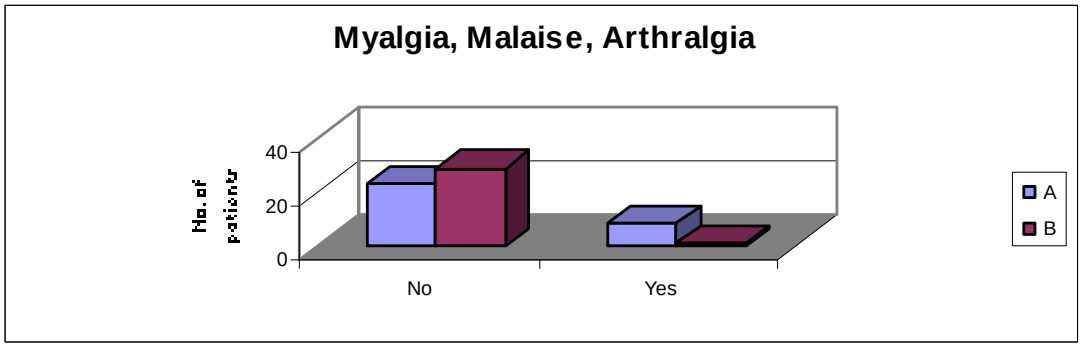


Table 19: Cystitis, dysuria

CYSTITIS,DYSURIA, FREQUENCY,URGENCY	NO OF PATIENTS	DISCOMFORT SCORE
GROUP A	31	4.16
GROUP B	30	2.6

Marked by patients on a visual analogue scale of 1 to 5 with one being the least troublesome and 5 the worst.

We have already shown that BCG + IFN combination is as efficacious as BCG alone, but when we consider the side effect profile and toxicity of both the groups we can see that BCG + IFN is significantly better in all respects. None of the patients had any serious side effects like BCGosis etc that necessitated stoppage of treatment. No patient needed to be started on Anti tuberculosis treatment

Less hematuria, less cystitis like features, less myalgia, arthralgia and malaise with more than 80% not having fever group B has a much lower side effect profile.

This in turn has two significant benefits

1. It reduces the number of physician visits that the patient has to undergo because of the treatment related side effects.
2. Symptomatic therapy for the side effects is also reduced thereby saving both man-hours as well as the cost of drugs

But this has to be weighed against the increased cost of the BCG + IFN combination.

BCG 60 mgs + IFN (6 miu) = Rs 1600

BCG 120 mgs = Rs 750.

If cost was not included in the equation then the patient should always prefer an equally effective but less toxic. Therapy = BCG + IFN

The limitations of the study are the small study population and limited follow up.To reach definitive conclusions we need to have a multicentric trial with a larger study population and a much longer follow up because bladder cancer natural history is such that definitive conclusions need more follow up

CONCLUSION

BCG (60 mgs) + IFN alpha 2b (6 Miu) combinations is equally if not better effective than BCG (120 mgs) alone as intravesical therapy for superficial bladder cancer.

Side effects of the combination therapy are significantly better for the combination treatment though its cost is also higher when compared to BCG alone.

Definitive role for IFN + BCG combination as a first line therapy exists.

Larger multicentric trials with a bigger study population and longer follow up are required to come to definitive conclusions.

BIBILIOGRAPHY:

1. Hudson MA, Herr HW: Carcinoma in situ of the bladder. J Urol 153 (3 Pt 1): 564-72, 1995.

2. Torti FM, Lum BL: The biology and treatment of superficial bladder cancer. J Clin Oncol 2 (5): 505-31, 1984.

3. Lacombe L, Dalbagni G, Zhang ZF, et al.: Overexpression of p53 protein in a high-risk population of patients with superficial bladder cancer before and after bacillus Calmette-Guérin therapy: correlation to clinical outcome. J Clin Oncol 14 (10): 2646-52, 1996.

4. Stein JP, Grossfeld GD, Ginsberg DA, et al.: Prognostic markers in bladder cancer: a contemporary review of the literature. J Urol 160 (3 Pt 1): 645-59, 1998.

5. Witjes JA, Caris CT, Mungan NA, et al.: Results of a randomized phase III trial of sequential intravesical therapy with mitomycin C and bacillus Calmette-Guerin versus mitomycin C alone in patients with superficial bladder cancer. J Urol 160 (5): 1668-71; discussion 1671-2, 1998.

6. Thrasher JB, Crawford ED: Current management of invasive and metastatic transitional cell carcinoma of the bladder. J Urol 149 (5): 957-72, 1993.

7. Esrig D, Elmajian D, Groshen S, et al.: Accumulation of nuclear p53 and tumor progression in bladder cancer. N Engl J Med 331 (19): 1259-64, 1994.

8. Lipponen PK: Over-expression of p53 nuclear oncoprotein in transitional-cell bladder cancer and its prognostic value. Int J Cancer 53 (3): 365-70, 1993

9. HolmÃ¤ng S, Hedelin H, AnderstrÃ¶m C, et al.: The relationship among multiple recurrences, progression and prognosis of patients with stages Ta and T1 transitional cell cancer of the bladder followed for at least 20 years. J Urol 153 (6): 1823-6; discussion 1826-7, 1995.

10. Smits G, Schaafsma E, Kiemeney L, et al.: Microstaging of pT1 transitional cell carcinoma of the bladder: identification of subgroups with distinct risks of progression. Urology 52 (6): 1009-13; discussion 1013-4, 1998.

11. Igawa M, Urakami S, Shirakawa H, et al.: Intravesical instillation of epirubicin: effect on tumour recurrence in patients with dysplastic epithelium after

transurethral resection of superficial bladder tumour. Br J Urol 77 (3): 358-62, 1996.

12. Lacombe L, Dalbagni G, Zhang ZF, et al.: Overexpression of p53 protein in a high-risk population of patients with superficial bladder cancer before and after bacillus Calmette-GuÃ©rin therapy: correlation to clinical outcome. J Clin Oncol 14 (10): 2646-52, 1996.

13. Herr HW: The value of a second transurethral resection in evaluating patients with bladder tumors. J Urol 162 (1): 74-6, 1999.

14. Herr HW, Schwalb DM, Zhang ZF, et al.: Intravesical bacillus Calmette-GuÃ©rin therapy prevents tumor progression and death from superficial bladder cancer: ten-year follow-up of a prospective randomized trial. J Clin Oncol 13 (6): 1404-8, 1995.

15. Sarosdy MF, Lamm DL: Long-term results of intravesical bacillus Calmette-Guerin therapy for superficial bladder cancer. J Urol 142 (3): 719-22, 1989

16. Coplen DE, Marcus MD, Myers JA, et al.: Long-term followup of patients treated with 1 or 2, 6-week courses of intravesical bacillus Calmette-Guerin: analysis of possible predictors of response free of tumor. J Urol 144 (3): 652-7, 1990.

17. Catalona WJ, Hudson MA, Gillen DP, et al.: Risks and benefits of repeated courses of intravesical bacillus Calmette-Guerin therapy for superficial bladder cancer. J Urol 137 (2): 220-4, 1987.

18. Herr HW: Progression of stage T1 bladder tumors after intravesical bacillus Calmette-Guerin. J Urol 145 (1): 40-3; discussion 43-4, 1991.

19. Lamm DL, Blumenstein BA, Crawford ED, et al.: A randomized trial of intravesical doxorubicin and immunotherapy with bacille Calmette-GuÃ©rin for transitional-cell carcinoma of the bladder. N Engl J Med 325 (17): 1205-9, 1991.

20. Lamm DL, Crawford ED, Blumenstein B, et al.: Maintenance BCG immunotherapy of superficial bladder cancer: a randomized prospective Southwest Oncology Group study. [Abstract] Proceedings of the American Society of Clinical Oncology 11: A-627, 203, 1992.

21. Rintala E, Jauhiainen K, Kaasinen E, et al.: Alternating mitomycin C and bacillus Calmette-Guerin instillation prophylaxis for recurrent papillary (stages Ta to T1) superficial bladder cancer. Finnbladder Group. J Urol 156 (1): 56-9; discussion 59-60, 1996.

22. Witjes JA, Caris CT, Mungan NA, et al.: Results of a randomized phase III trial of sequential intravesical therapy with mitomycin C and bacillus Calmette-Guerin versus mitomycin C alone in patients with superficial bladder cancer. J Urol 160 (5): 1668-71; discussion 1671-2, 1998.

23. MalmstrÃ¶m PU, WijkstrÃ¶m H, Lundholm C, et al.: 5-year followup of a randomized prospective study comparing mitomycin C and bacillus Calmette-Guerin in patients with superficial bladder carcinoma. Swedish-Norwegian Bladder Cancer Study Group. J Urol 161 (4): 1124-7, 1999.

24. Soloway MS: The management of superficial bladder cancer. In: Javadpour N, ed.: Principles and Management of Urologic Cancer. 2nd ed. Baltimore, Md: Williams and Wilkins, 1983., pp 446-467.Â

25. Herr HW, Reuter VE: Evaluation of new resectoscope loop for transurethral resection of bladder tumors. J Urol 159 (6): 2067-8, 1998.

26. Amling CL, Thrasher JB, Frazier HA, et al.: Radical cystectomy for stages Ta, Tis and T1 transitional cell carcinoma of the bladder. J Urol 151 (1): 31-5; discussion 35-6, 1994.

27. Goffinet DR, Schneider MJ, Glatstein EJ, et al.: Bladder cancer: results of radiation therapy in 384 patients. Radiology 117 (1): 149-53, 1975.

28. van der Werf-Messing B, Hop WC: Carcinoma of the urinary bladder (category T1NxM0) treated either by radium implant or by transurethral resection only. Int J Radiat Oncol Biol Phys 7 (3): 299-303, 1981.

29. Lamm DL, Riggs DR, Shriver JS, et al.: Megadose vitamins in bladder cancer: a double-blind clinical trial. J Urol 151 (1): 21-6, 1994.

30. Crispen R: History of BCG and its substrains;in Debruyne FMS, Denis L, van der MeijdenAPM (eds): BCG in superficial bladder cancer.EORTC Genitourinary group Monograph 6.New York, Alan R Liss, 1989, pp 35-50.

31. de Kernion JB, Golub SH, Gupta RK, Silver-steinM, Morton DL: Successful transurethral intralesional BCG therapy of bladder mel-anoma.Cancer 1975;36:1662-1664.
32. Bloomberg SD, Brosman SA, Hausman MS,Cohen A, Battenberg JD: The effect of BCG on the dog bladder. Invest Urol 1975;12: 423426.
33. Lamm DL, Harris SC, Gittes RF: Bacillus Cal-mette-Guérin and dinitrochlorobenzene immunotherapy of chemically induced bladder tumors. Invest Urol 1977;14:369-372.
34. Morales A, Eidinger D, Bruce AW: Intracavi-tary bacillus Calmette-Guérin in the treatment of superficial bladder tumors. J Urol 1976;116: 180-183.
35. Lamm DL, Thor DE, Harris SC, Reyna JA, Radwin HM: BCG Immunotherapy of superficial recurrent bladder cancer. Proceedings AUA 1979;74:97.
36. Pinsky CM, Camacho FJ, Kerr D, Braun DW,Whitmore SF, Oettgen HF: Treatment of superficial bladder cancer with intravesical BCG; in Terry WD, Rosenberg SA (eds): Immunotherapy of human cancer. New York, Elsevier, 1982, pp 310-313.

37. Reynolds RH, Stogdill VD, Lamm DL: Disease progression in BCG treated patients with transitional cell carcinoma of the bladder. J Urol 1985;133:211A.
38. Herr HW, Laudone VP, Badalament RA, Oettgen HF, Sogani PC, Freedman BD, Melamed MR, Whitmore WF: BCG therapy alters the progression of superficial bladder cancer. Oncol 1988;6:1450-1455.
39. Pagano F, Bassi P, Milani C, Meneghini A, Maruzzi D, Garbeglio A: A low dose bacillus Calmette-Guerin regimen in superficial bladder cancer therapy: Is it effective? J Urol 1991; 146:32-35
40. Davies, M.: Bacillus Calmette-Guerin as an antitumor agent. The interaction with cells of the mammalian immune system. Biochem Biophys Acta. 1982;651:143.
41. DeBoer, E.C., DeJong, W.H., Steerenberg, P.A., et al,: Induction of urinary interleukin-1 (IL-1), IL-2, IL-6, and tumor necrosis factor during intravesical immunotherapy with bacillus Calmette-Guerin in superficial bladder cancer. Cancer Immunol Immunother 1992; 34:306-312.
42. McAveray, D.M., Gomella, L.G., Lattime, E.C.: Cytokin regulation of antitumor immunity following localized immunotherapy of bladder cancer. (Abstract) Proceedings of the 85th Annual Meeting of the American Association for Cancer Research; 1994 April 10-13; San Francisco, (CA):35:A2863.
43. Ratliff, T.L., Ritchey, J.K., Yaun, J.J., et al.: Role of CD4 and CD8 lymphocytes in the antitumor activity of BCG. J Urol 1993; 150:1018-1023.
44. Sosnowski, J.T., Lamm, D.L.: Immunotherapy for bladder cancer. In Rous SN, ed. Urology Annual, East Norwalk, Connecticut: Appleton & Lange; 1990;4:123-156.
45. Morales, A., Ottenhof, P.C.: Clinical application of a whole blood assay for human natural killer (NK) cell activity. Cancer. 1983;52:667.
46. Conti, P., Reale, M., Nicolai, M., et al: Bacillus Calmette-Guerin potentiates monocytes responses to lypopolsaccharide-induced tumor necrosis factor and interleukin-1, but notinterleukin-6 in bladder cancer patients. Cancer Immunol Immunother 1994;38:365-271.
47. Ratliff, T.L., Gillen, D., Catalona, W.J.: Requirement of a thymus dependent immune response for BCG-mediated antitumor activity. J Urol. 1987;137:155.
48. Ratliff, T.L., Hudson, M.A., Catalona, W.J.: Strategy for improving therapy of superficial bladder cancer. World J Urol. 1991;9:95.
49. Becich, M.J., Carroll, S., Ratliff, T.L.: Internalization of Bacille Calmette-Guerin by bladder tumor cells. J Urol. 1991;145:1316.
50. Kuroda, K., Brown, E.J., Telle, W.B., et al: Characterization of the internalization of bacillus Calmette-Guerin by human bladder tumor cells, J Clin Invest 1993;91:69-76.
51. Morales, A., Nickel, J.C.: Immunotherapy of superficial bladder cancer with BCG. World J Urol 1986;3:209-214.
52. Garden, R.J., Liu, B.C.S., Redwood, S.M., et al.: Bacillus Calmette-Guerin abrogates in vitro invasion and motility of human bladder tumor cells via fibronectin interaction. J Urol. 1992;148:900.
53. Schmidt, A.C., Bouic, P.J., Heyns, C.F., DeKock, M.L.: Peripheral blood lymphocyte response in patients with superficial transitional cell carcinoma of the

bladder treated with intravesical bacillus Calmette-Guerin - a useful marker of response? Br J Urol 1993;71:179-182.
54. Winters, W.D., Lamm, D.L.: Antibody responses to bacillus Calmette-Guerin during immunotherapy in bladder cancer patients. Cancer Res 1981;41:2672-2676.
55. Lamm, D.L., Reichart, D.F., Harris, S.C., Lucio, R.M.: Immunotherapy of murine transitional cell carcinoma, J Urol 128:1104, 1982.
56. Corti Ortiz, D., Rivera, Garay, P., Aviles Jasse, J., et al: (Prophylaxis of superficial bladder cancer with 1 mg of intravesical BCG: comparison with other doses). (Spanish) Actas Urol Esp 1993; 17:239-242.
57. Ratliff, T.L., Kavoussi, L.R., Catalona, W.J.: Role of fibronetin in intravesical BCG therapy for superficial bladder cancer. J Urol 188; 139:410-414.
58. Hudson, M.A., Yvan, J.J., Catalona, W.J., Ratliff, T.L.: Adverse effect of fibrin clot inhibitors on intravesical bacillus Calmette-Guerin therapy for superficial bladder tumors. J Urol 1990; 144:1362-1364.
59. Rogerson, J.W.: Intravesical bacille Calmette-Guerin in the treatment of superficial transitional cell carcinoma of the bladder. Br J Urol 1994; 73:655-658.
60. DeBoer, L.C., Steerenberg, P.A., Van der Meijden, P.M., et al: Impaired immune response by isoniazid treatment during intravesical BCG treatment in the guinea pig. J Urol 1992; 148:1477-1582,
61. Stassar, M.J., Vegt, P.D., Steerenber, P.A., et al.: Effects of isoniazid (INH) on the BCG-induced local immunotherapy response after intravesical BCG therapy for superficial bladder cancer. Urol Res 1994; 22:177-184.
62. Lamm, D.L.: (1992) Long-term results of intravesical therapy for superficial bladder cancer. In Lamm DL, ed. The Urologic Clinics of North America, Philadelphia, PA: W.B. Saunders Co.; 19:573-580.
63. Nadler, R.B., Catalona, W.J., Hudson, M.A., Ratliff, T.L.: Durability of tumor-free response for intravesical bacillus Calmette-Guerin therapy. J Urol 1994; 152(2 Pt 1):367-373.
64. Herr, H.W.: Transurethral resection and intravesical therapy of superficial bladder tumors. In Fair WR, ed. The Urologic Clinics of North America, Philadelphia, PA: W.B. Saunders Co.; 1991; 18:525-528.
65. Lamm, D.L.: (1985) Bacillus Calmette-Guerin immunotherapy for bladder cancer. Journal of Urology. 134:40-47.
66. Herr, H.W., Pinsky, C.M., Whitmore, W.F., et al.: Experience with intravesical Bacillus Calmette-Guerin therapy of superficial bladder tumors. Urology 1985; 25:119.
67. Herr, H.W., Pinsky, C.M., Whitmore, W.F., et al.: Long-term effect of intravesical Bacillus Calmette-Guerin on flat carcinoma in situ of the bladder. J Urol 1986; 135:265.
68. Pagano, F., Bassi, P., Milani, C., et al.: A low dose bacillus Calmette-Guerin regimen in superficial bladder cancer therapy: Is it effective?. J Urol. 1991;146:32.
69. Melekos, M.D., Chionis, H., Pantazakos, A., Fokaefs, E., Paranychianakis, G., and Dauaher, H.: Intravesical Bacillus Calmette-Guerin Immunoprophylaxis Of

Superficial Bladder Cancer: Results Of A Controlled Prospective Trial With Modified Treatment Schedule. J Urol 1993;149:744.
70. Krege, S., Giani, G., Meyer, R., et al.: A randomized multicenter trial of adjuvant therapy in superficial bladder cancer: transurethral resection only versus transurethral resection plus mitomycin versus transurethral resection plus Bacillus Calmette-Guerin. J Urol 1996; 156: 962-6.
71. Rodriques Netto Junior, N., Lemos, G.C.: A comparison of treatment methods for prophylaxis of recurrent superficial bladder tumors. J Urol 1983; 129:33-34.
72. Martinez-Pineiro, J.A., Leon, J.J., Martinez-Pineiro, L. Jr., Fiter, L., Mosteiro, J.A., Navarro, J., Garcia, Matres, M.J., Carcamo: Bacillus Calmette-Guerin versus Doxorubicin versus Thiotepa: A randomized prospective study in 202 patients with superficial bladder cancer. Journal of Urology 1990;143:502-506.
73. Debruyne, F.M.J., Van der Meijden, A.P., Goebers, A.D.H., et al.: BCG-RIVM versus mitomycin intravesical therapy in superficial bladder cancer first results of a randomized prospective trial. Urology (suppl) 1988; 31:20-25.
74. Jauhianen, K., Rintala, E., Alfthan, O., and the Finnbladder Group: Immunotherapy (BCG) versus chemotherapy (MMC) in intravesical treatment of superficial urinary bladder cancer. In deKernion JB, ed. Immunotherapy of Urological Tumors, Edinburgh: Churchill Livingston, 1990, 13-60.
75. Rubben, H., Graf-Dobberstein, C., Ostwald, R., et al.: Prospective randomized study of adjuvant therapy after complete resection of superficial bladder cancer; mitomycin C vs. BCG Connaught vs. TUR alone. In deKernion JB, ed. Immunotherapy of Urological Tumors, Edinburgh: Churchill Livingstone; 1990;27-36.
76. Witjes, J.A., Van der Meijden, A.P., Witjes, J.P., et al.: Randomized prospective study comparing intravesical instillations of mitomycin-C, BCG-TICE, and BCG-RIVM in Pta-Pt1 tumors and primary carcinoma in situ of the urinary bladder. Dutch South-East Cooperative Group. Eur J Cancer 1993;29A:1672-1676.
77. Lamm, D.L., Crawford, E.D., Blumenstein, B., et al.: SWOG 8795: A randomized comparison of bacillus Calmette-Guerin and mitomycin-C prophylaxis in stage Ta and T1 transitional cell carcinoma of the bladder. Urol Oncol 1995; 1:119-126.
78. Huland, H., Otto, U.: Use of mitomycin as prophylaxis following endoscopic resection of superficial bladder cancer. Urology 1985; 26(4 Suppl):32-35.
79. Melekos, M.D., Chionis, H.S., Paranychianakis, G.S., Dauaher, H.H.: Intravesical 4'-epi-doxorubicin (epirubicin) versus bacillus Calmette-Guerin. A controlled prospective study on the prophylaxis of superficial bladder cancer. Cancer 1993; 72:1749-1755.
80. Cookson, M.S., Sarosdy, M.F.: Management of stage T1 superficial bladder cancer with intravesical bacillus Calmette-Guerin therapy. Journal of Urology. 1992;148:797-801.
81. Herr, H.W., Laudone, V.P., Badalament, R.A., et al.: Bacillus Calmette-Guerin therapy alters the progression of superficial bladder cancer. J Clin Oncol 1988; 6:1450-1455.
82. Witjes, J.A., Fransen, M.P., Van der Meijden, A.P., et al.: use of maintenance intravesical bacillus Calmette-Guerin (BCG), with or without intradermal BCG,

in patients with recurrent superficial bladder cancer. Long-term follow-up of a randomized phase 2 study. Urol Int 1993; 51:67-72.
83. Lamm, D.L.: Carcinoma in situ (review) Urol Clin North Amer. 1992; 19:499-508.
84. Lamm, D.L., Blumenstein, B.A., Crawford, E.D., Montie, J.E., Scardino, P., Grossman, H.B., Stanisic, T.H., Smith, H.A., Sullivan, J., Sarosdy, M.F., Crissman, J.D., and Coltman, C.A.: A randomized trial of intravesical doxorubicin and immunotherapy with Bacille Calmette-Guerin for transitional cell carcinoma of the bladder. New Engl J Med. 1991, 325(17):1205-1209
85. Lamm, D.L., Riggs, D., Shriver, J., Van Gilder, P., Rach, J., DeHaven, J.: Megadose vitamins in bladder cancer: A double-blind clinical trial. J Urol 1994;151:21-26.
86. Lamm D.L.: Complications of bacillus Calmette-Guerin immunotherapy. (Review) Urol Clin North Am 1992; 19:565-572.
87. Berry D.L., Blumenstein B.A., Magyary D.L., et al.: Local toxicity patterns associated with intravesical bacillus Calmette-Guerin: A Southwest Oncology Group Study. Int J Urol 1995; 3:98-101.
88. Koukol, S.C., DeHaven, J.I., Riggs, D.R., Lamm, D.L.: Drug therapy of bacillus Calmette-Guerin sepsis. Urol Res 1995; 22:373-376.
89. Bowyer, L., Hall, R.R., Reading, J., March M.M.: The persistence of bacille Calmette-Guerin in the bladder after intravesical treatment of bladder cancer. Br J Urol 1995; 75:199-192.
90. Kristjansson, M., Green, P., Manning, H.L., RD, et al.: Molecular confirmation of bacillus Calmette-Guerin as the cause of pulmonary infection following urinary tract instillation. Clin Infect Dis 1993; 17:228-230.
91. Torti, F.M., Shortliffe, L.D., Williams, R.D., Pitts, W.C., Kempson, R.L., Ross, J.C., Palmer, J., Meyers, F., Ferrari, M., Hannigan, J., Spiegel, R., McWhirter, K., and Freihia, F.: Alpha-Interferon in superficial bladder cancer: A northern California oncology group study. J Clin Oncol 1988;6:476.
92. Brosman SA: Experience with bacillus Cal-mette-Guérin in patients with superficial bladder carcinoma. J Urol 1982;128:27-30.
93. Netto NR, Lemos GCD: A comparison of treatment methods for the prophylaxis of recurrent superficial bladder tumors. J Urol 1983;129:33-34.
94. Lamm DL, Crissman J, Blumenstein B, Crawford ED, Montie J, Smith J, Sullivan J, Sarosdy M: Adriamycin versus BCG in superficial bladder cancer: a Southwest Oncology Group study; in Debruyne FMS, Denis L, van der Meijden APM (eds): BCG in superficial bladder cancer. EORTC Genitourinary group Monograph 6. New York, Alan R Liss, 1989, pp 263-270.
95. Lamm DL, Blumenstein BA, Crawford ED, Montie JE, Scardino P, Grossman HB, Stanisic TH, Smith JA, Sullivan J, Sarosdy MF, Crissman JD, Coltman CA: A randomized trial of intravesical doxorubicin and immunotherapy with bacillus Calmette-Guérin for transitional cell carcinoma of the bladder. N Engl J Med 1991;325:1205-1209.
96. Kavoussi LR, Torrence RJ, Gillen DP, Hud- 28 son MA, Haaff EO, Dresner SM, Ratliff TL, Catalona WJ: Results of 6 weekly intravesical bacillus Calmette-

Guerin instillations on the treatment of superficial bladder tumors. J Urol 1988;139:935-939.
97. Lamm DL, Reichert DF, Harris SC, Lucio RM: Immunotherapy of transitional cell carcinoma. J Urol 1982;128:1106-1110.
98. Lamm DL: Bacillus Calmette-Guérin immunotherapy for bladder cancer. J Urol 1985;134: 40-47.
99. Badalament RA, Herr HW, Wong GY, Gnecco C, Pinsky CM, Whitmore WF, Fair WR, Oettgen HF: A prospective randomized trial of maintenance versus nonmaintenance intravesical bacillus Calmette-Guérin therapy of superficial bladder cancer. J Clin Oncol 1987;5:441-449.
100. Hudson MA, Ratliff TL, Gillen DP, HaaffEO, Dresner SM, Catalona WJ: Single course versus maintenance bacillus Calmette-Guérin therapy for superficial bladder tumors: A pro-spective randomized trial. J Urol 1987;138: 295-298.
101. Reichert DF, Lamm DL: Long term protection in bladder cancer following intralesional immunotherapy. J Urol 1984;132:570-573.